

# Long-term outcome of ten children with opsoclonus-myoclonus syndrome

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**Abstract** Opsoclonus-myoclonus syndrome (OMS) in children is a rare neurological condition with opsoclonus, myoclonus, ataxia and irritability in the first 2 years of life. It can be idiopathic, parainfectious, or paraneoplastic with tumours of the neural crest. Few studies of long-term follow-up after OMS have been published. We investigated the motor, cognitive and behavioural outcome of ten patients (eight girls and two boys) seen between 1987 and 2002. We reviewed the records and reassessed the patients. A ganglioneuroma was found in one patient and a neuroblastoma in another. Tumour resection did not influence the OMS. The age at diagnosis was 10–24 months and the follow-up period 1–17 years (average 6.5 years). The interval between the first signs and symptoms and starting treatment was 2–12 weeks: treatment consisted of different immunosuppressants. Remission was achieved within 5 months in seven, and relapses were present in seven of ten. At follow-up, only one child had mild ataxia. IQ testing was performed in nine with scores below 75 in four and above 85 in four. Attention deficit and visuomotor difficulties led to school problems with special needs, also in those three children with normal IQs. Only two children were attending regular schools. Behavioural problems were reported in seven, and speech difficulties were present in five. In conclusion, the long-term outcome in our patients with OMS was dominated by cognitive and behavioural problems and not by ataxia. Compared with previous reports, our patients were treated earlier. Larger studies and uniform treatment protocols are needed to demonstrate

whether early and prolonged immunosuppressant therapy has a favourable influence on outcome.

**Keywords** Opsoclonus-myoclonus syndrome · Dancing eye syndrome · Ataxia · Long-term follow-up · Neuroblastoma

## Abbreviations

OMS	opsoclonus-myoclonus syndrome
CBCL	child behaviour checklist
IVIG	intravenous immunoglobulin
CSA	cyclosporin A
MRI	magnetic resonance imaging
IQ	intelligence quotient

## Introduction

Opsoclonus-myoclonus syndrome (OMS) in childhood is a rare neurological condition with an acute onset of myoclonus, opsoclonus, and ataxia. Opsoclonus is defined as repetitive involuntary, irregular, rapid conjugate eye movements, often precipitated by saccades. Myoclonia are multifocal small-amplitude muscle jerks frequently accompanied by cerebellar ataxia. There is a rapid loss of motor control and speech, and regression from developmental milestones. The children are highly irritable and already have severe sleep disturbances in the prodromal phase [17]. In contrast to OMS, acute post-infectious cerebellar ataxia is never accompanied by either myoclonia or opsoclonus and rarely by irritability. OMS usually occurs in the first 2 years of life and is associated with viral infections or tumours of the neural crest. Only about 2–3% of patients with neuroblastoma have paraneoplastic OMS, and their survival is substantially longer than in children with

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neuroblastoma without OMS [22]. Neuroblastoma in the presence of OMS is usually low stage with favourable histology, normal catecholamine excretion, and a single copy of the *n-myc* oncogene.

The aetiology of OMS is still debated. There is strong evidence for it being an antibody-mediated disease, but so far no specific autoantibody has been found [2, 3, 9, 20].

Reported treatment options include oral corticosteroids, high-dose methylprednisolone, corticotropin (ACTH), intravenous immunoglobulin, cyclophosphamide and plasmapheresis. Recently, Pranzatelli et al. reported a good response to rituximab [19].

The long-term neurological outcome in patients with OMS has been studied in patients with associated neuroblastoma [7, 8, 13, 15]. There are also studies of mixed populations, including patients with OMS of paraneoplastic or parainfectious origin [6, 12, 14, 16, 24]. The reports of long-term outcome include descriptions of persistent and disabling ataxia, speech abnormalities, behavioural problems, and learning disabilities of differing severity and frequency. No correlation between the outcome and the response to therapy or removal of the tumour has yet been found [7, 13, 15, 16, 24]. A recent longitudinal study showed a correlation between the outcome and course of the disease, with a worse outcome in patients with multiple relapses [12].

We were interested in the long-term outcome in our patients, focussing particularly on motor, cognitive and behavioural problems.

## Patients and methods

The medical records of patients with OMS seen between 1987 and 2002 were reviewed and the patients reassessed by interview and neurological examination. Nine of ten had additional neuropsychological testing.

Ataxia and dysmetria were graded as severe, moderate, mild or minimal according to the degree of the disturbance of activities of daily living: severe: unable to walk unassisted; moderate: wide-based gait, frequent falls, and overt dysmetria; mild: infrequent falls, gross motor problems, and fine motor difficulties in drawing or writing; minimal: no gait ataxia or dysmetria on neurological examination, but the children were outside the age-specific normal range in the pegboard and equilibrium subtest of the Zurich Neuromotor Assessment [10].

When possible, developmental status and cognitive function were tested according to age with SON-R [25], HAWIVA [5] or HAWIK-III [26].

Behavioural problems were assessed by parent interview and with the Child Behavior Checklist (CBCL) [1, 4].

## Results

Between 1987 and 2003, ten patients (eight girls and two boys) with OMS were seen. A retroperitoneal neuroblastoma was diagnosed in one patient, and a retroperitoneal ganglioneuroma in another. The age at diagnosis was 10–24 months (mean, 18 months). During the acute stage, all patients showed opsoclonus, myoclonus and ataxia; eight patients were unable to sit, and two were able to walk with assistance. All were highly irritable and had disturbed sleep. Two lost speech for several weeks.

Therapy was started 2–12 weeks (median, 3 weeks) after the onset of symptoms; oral prednisolone was the first step in all patients. Intravenous immunoglobulin (IVIG) was given subsequently in six patients because of symptom relapses or prednisolone dependence. Two were treated with high-dose methylprednisolone (3 days of 30 mg/kg/day and 50 mg/kg/day, respectively) and IVIG (six to eight cycles at 4–8-week intervals) with good effect. One patient was treated with cyclophosphamide and three with azathioprine. In two patients, cyclosporin A had a good effect on opsoclonus and myoclonus with persisting ataxia, and in one patient a relapse with ataxia and opsoclonus responded to cyclosporin A. A first remission of opsoclonus and myoclonus under immunosuppressant medication was achieved in less than 5 months in seven patients. Relapses, defined by worsening of ataxia, opsoclonus and myoclonus after first remission, were present in four of seven. In the remaining three patients, symptoms were only partially controlled over 12–24 months, and they also suffered relapses (Table 1). Two patients were still being treated with cyclosporin A at the time of re-evaluation.

### Re-evaluation (see also Table 1)

The interval between the onset of OMS and re-evaluation was 1–17 years (mean 6.5 years). The age at reassessment was 3 to 17.7 years.

### Ataxia

Five of ten had no ataxia and were age appropriate in the pegboard and equilibrium test of the Zurich Neuromotor Assessment test. Four of ten were graded as having minimal ataxia; they had no gait ataxia and no difficulties in everyday life, but were not age appropriate in the equilibrium test. Only one 5-year-old girl had mild gait ataxia.

### Dysmetria

Five of ten were within the normal range of the age-specific norms for the pegboard test. Five of ten did not reach this

**Table 1** Summary of neurological and neuropsychological outcome at re-evaluation

Age at re-evaluation (in years)	Age at onset (years)	Disease course	Ataxia	Dysmetria	Speech	IQ	School	Behaviour CBCL T scores
3	1.5	Monophasic	No	No	Normal	n.t.		y
*3.4	1.9	Monophasic	No	No	Normal	>85		y
5	1.0	>14 months rl	Mild	Mild	Dysarthria	<75	Special school	64
5.1	1.9	>14 months rl	Minimal	Minimal	Dysarthria	<75	Special school	61
**7	1.9	rl	Minimal	Minimal	Normal	<75	Special class	62
7	1.4	rl	Minimal	Minimal	Normal	75–85	Special school	73
7.9	2.0	Monophasic	No	No	Slurred	>85	Special class	62
11.5	1.2	rl	No	No	Normal, x	>85	Regular	39
12	1.1	rl	No	Minimal	Slurred	>85	Regular	63
17.7	0.8	>24 months rl	Minimal	No	Dysarthria	<50	Special school	60

\*neuroblastoma associated, \*\* ganglioneuroma associated

Disease course: monophasic: symptom control within 5 months, no relapses; rl: multiple relapses; >14, 24 months, respectively: no remission of opsoclonus and myoclonus during that time on various medications.

n.t.: not tested

x: speech therapy earlier.

Special school: school for learning-disabled children, special class: class with fewer pupils but regular academic goals.

Behaviour: y: CBCL not applicable due to young age, but no problem evident at interview.

Normative mean of CBCL T scores: 50, SD 10, >60: borderline, >70 clinically significant behavioural problem.

range, but only the girl with mild gait ataxia had difficulties in daily living because of fine motor problems.

### Speech

Four of ten had a hoarse voice; expressive speech abnormalities such as a slightly slurred speech, articulation problems or word-finding difficulties were present in five of ten; three were difficult to understand, and one had needed speech therapy earlier.

### Cognitive performance

Nine patients were tested. The IQ was >85 in four of eight, in one patient it was between 75 and 85, and four of eight had an IQ <75. A 3-year-old child was not tested, but was age appropriate clinically.

### School performance

Two children were not yet of school age. Although four of eight had a normal IQ, only two were able to attend regular school: four of ten needed special education for learning disabled children, and two attended a special class of longer duration with fewer pupils, but with regular academic aims.

### Behaviour

In the interview, eight of ten children were described by the parents as more difficult than their siblings or peers. Mainly, they were impulsive, aggressive and emotionally

unstable. In the Child Behavior Checklist (Achenbach CBCL), two children had normal results (normative mean 50, SD 10), five of ten had borderline scores between 60 and 63, and two had T scores >63; one scored 73, which is considered to be clinically significant problematic behaviour, with externalising symptoms predominating. In two children the CBCL questionnaire was not applicable because of their age, but they were described as easy children by the parents. In the subtests, five of ten had signs of attention problems.

### Neuroimaging

A cerebral MRI was performed in two children, 8 and 16 years after the acute stage, demonstrating moderate and mild atrophy of the cerebellar hemispheres and vermis, respectively. At the time of the investigation both children had only mild ataxia; the girl with moderate atrophy had an IQ <50 whilst the boy attended regular school.

## Discussion

The long-term neurological outcome of patients with OMS has been studied in patients with associated neuroblastoma [7, 8, 13, 15] and in mixed populations of patients with OMS of paraneoplastic, “idiopathic” or parainfectious origin [6, 14, 16, 24]. In these reports, paraneoplastic OMS was seen in 7–90% of the patients. In studies with US patients [6, 24], 41–90% were reported to have paraneoplastic OMS compared with 7% in a larger European study

[16]. This may be due to less extensive investigation or to genetic factors. Only two of our patients had an associated tumour of the neural crest. This corresponds to the ratio of paraneoplastic and “idiopathic” OMS in European studies. Tate et al. compared patients with paraneoplastic and idiopathic OMS and did not find any difference in the age of onset, course and neurological outcome [24].

Regarding the long-term outcome, persistent and disabling ataxia, speech abnormalities, behavioural problems, and learning disabilities have been described. Most studies had patient numbers between 10–21, but the largest series (by Tate et al. [24] and Pohl et al. [16]) had 105 and 54 patients, respectively. The longest follow-up in a single report was 41 years [18]. Complete recovery was seen in only 12%–38% of the children [15, 16].

No correlation between outcome and response to therapy, or removal of the tumour [7, 13, 15, 16, 24], or delay in treatment has been found [8, 13, 16]. The interval between the onset of symptoms and initiation of treatment was 10.9 weeks (median) in the study by Pohl et al. [16], and ranged from 1 week to 30 months (median 4 months) in the study by Mitchell et al. [13]. The interval between onset and diagnosis was 6 weeks to 1 year in the study by Koh et al. [8], 1–24 weeks (median 6 weeks) in the study by Plantaz et al. [15], and an average of 3 months in the study by Tate et al. [24]. In our group of patients diagnosis was made much more rapidly and therapy was started immediately regardless of tumour evaluation (median interval, 3 weeks). In one patient in whom treatment was delayed for 12 weeks, there were more significant motor and cognitive sequelae, and symptoms were difficult to control. The three children who had a long-lasting and severe acute phase with worsening of symptoms during infections or tapering of steroid dose over 12–24 months demonstrated a worse long-term outcome, especially in cognition and behaviour. Mitchell et al. [12] reported a better outcome in children with a monophasic course of the disease. In our group, seven children had relapses later than 2 years after diagnosis, with variable control by immunosuppressant medication, and their outcome varied considerably between being able to attend regular school and having significant cognitive and behavioural sequelae. The three patients with a monophasic course had a good outcome; one had behavioural and speech problems. There was an overall tendency towards a better cognitive and behavioural outcome with better symptom control.

In terms of ataxia, our patients demonstrated a better outcome as compared with the cases in the literature [6, 8, 12–16]. As shown in Table 1, only one of our patients had mild ataxia at follow-up; four were graded as minimal with normal gait and no motor handicap in everyday life, but they were not age appropriate in standing on one leg. In some children, ataxia was prominent in the first 2–4 years,

but had improved impressively by school age. The better motor outcome may be due to faster initiation of treatment, but this remains speculative because of the small number of patients.

The cognitive, behavioural and language problems and attention deficit symptoms have been described as sequelae of OMS. Papero et al. [14] reported T scores of more than 60 in 7/8 of the children in the CBCL; IQ ranged from 50–87 and verbal fluency was disrupted in 12/13. In the study by Pohl et al. [16], 32/54 patients had a learning disability and 33/54 a speech abnormality. Hayward et al. [7] reported speech problems in 7/11, CBCL T scores >60 in 4/11, and IQ >1 SD below the mean in 5/11. Koh et al. [8] described problems in development including language deficits and inattention and behavioural problems in nine of ten. Mitchell et al. [13] reported IQ or developmental indices ranging from 44 to 94, with only 3/17 with an IQ in the normal range, and behavioural problems such as mood swings, tantrums, or opposition behaviour in 10/17; 4/17 children had CBCL scores >63, and all children had speech abnormalities. In their longitudinal study, 4/5 patients with a monophasic course were functioning in the average range of IQ and behaviour and adaptive skills: in the second assessment, 7/16 had scores >60 and 3 >63, and behavioural problems were stable compared with the previous examination. In the study by Tate et al., 40% of parents reported expressive language impairment and 25% behavioural problems as the largest remaining problem following OMS [24]. Cognitive, behavioural, attention and, to a lesser extent, speech problems were particularly prominent in our patients on long-term follow-up and also led to significant school problems in patients with normal IQs.

Problems in executive function (planning, verbal fluency, and working memory), spatial cognition (visual spatial organisation and memory), language and personality changes have been described as the cerebellar cognitive affective syndrome following lesions of the cerebellum (ischaemic lesions and tumour resections) [11, 21, 23]. The immunologic process of OMS may lead to changes in the cerebellum that are responsible for atrophy and the behavioural and cognitive problems on long-term follow-up.

Only two of our patients with a monophasic disease course had no residual problems, but they were the youngest, and therefore it may well be that subtle cognitive and behavioural problems are not yet detectable.

Concerning treatment, we report a good response in opsoclonus and myoclonus with persisting ataxia to cyclosporin A in two patients who were steroid dependant and who did not respond to IVIG; in one patient, a relapse was treated successfully with CSA, given because the parents were reluctant to start steroids again.

## References

- Achenbach TM (1991) Manual for the child behavior checklist 4–18 and 1991 profile. University of Vermont, Burlington, VT
- Antunes NL, Khakoo Y, Matthay KK, Seeger RC, Stram DO, Gerstner E, Abrey LE, Dalmau J (2000) Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 22:315–320
- Blaes F, Fuhlhuber V, Korfei M, Tschernatsch M, Behnisch W, Rostasy K, Hero B, Kaps M, Preissner KT (2005) Surface-binding autoantibodies to cerebellar neurons in opsoclonus syndrome. *Ann Neurol* 58:313–317
- Doepfner M, Melchers P, Fegert J, Lehmkuhl G, Lehmkuhl U, Schmeck K, Steinhausen HC, Poustka F (1994) Deutschsprachige Konsensus-Versionen der Child Behavior Checklist (CBCL 4–18), der Teacher Report Form (TRF) und der Youth Self Report Form (YSR). *Kindheit und Entwicklung* 3:54–59
- Eggert D, Schuck KD (1975) Hannover-Wechsler-Intelligenztest für das Vorschulalter (HAWIVA). Hans Huber, Bern
- Hammer MS, Larsen MB, Stack CV (1995) Outcome of children with opsoclonus-myoclonus regardless of etiology. *Pediatr Neurol* 13:21–24
- Hayward K, Jeremy RJ, Jenkins S, Barkovich AJ, Gultekin SH, Kramer J, Crittenden M, Matthay KK (2001) Long-term neurobehavioral outcomes in children with neuroblastoma and opsoclonus-myoclonus-ataxia syndrome: relationship to MRI findings and anti-neuronal antibodies. *J Pediatr* 139:552–559
- Koh PS, Raffensperger JG, Berry S, Larsen MB, Johnstone HS, Chou P, Luck SR, Hammer M, Cohn SL (1994) Long-term outcome in children with opsoclonus-myoclonus and ataxia and coincident neuroblastoma. *J Pediatr* 125:712–716
- Korfei M, Fuhlhuber V, Schmidt-Woll T, Kaps M, Preissner KT, Blaes F (2005) Functional characterisation of autoantibodies from patients with pediatric opsoclonus-myoclonus-syndrome. *J Neuroimmunol* 170:150–157
- Largo RH, Fischer JE, Rousson V (2003) Neuromotor development from kindergarten age to adolescence: developmental course and variability. *Swiss Med Wkly* 133:193–199
- Levisohn L, Cronin-Golomb A, Schmahmann JD (2000) Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain* 123:1041–1050
- Mitchell WG, Brumm VL, Azen CG, Patterson KE, Aller SK, Rodriguez J (2005) Longitudinal neurodevelopmental evaluation of children with opsoclonus-ataxia. *Pediatrics* 116:901–907
- Mitchell WG, Davalos-Gonzalez Y, Brumm VL, Aller SK, Burger E, Turkel SB, Borchert MS, Hollar S, Padilla S (2002) Opsoclonus-ataxia caused by childhood neuroblastoma: developmental and neurologic sequelae. *Pediatrics* 109:86–98
- Papero PH, Pranzatelli MR, Margolis LJ, Tate E, Wilson LA, Glass P (1995) Neurobehavioral and psychosocial functioning of children with opsoclonus-myoclonus syndrome. *Dev Med Child Neurol* 37:915–932
- Plantaz D, Michon J, Valteau-Couanet D, Coze C, Chastagner P, Bergeron C, Nelken B, Martelli H, Peyroulet MC, Carpentier AF, Armari-Alla C, Pagnier A, Rubie H (2000) Opsoclonus-myoclonus syndrome associated with non-metastatic neuroblastoma. Long-term survival. Study of the French Society of Pediatric Oncologists. *Arch Pediatr* 7:621–628
- Pohl KR, Pritchard J, Wilson J (1996) Neurological sequelae of the dancing eye syndrome. *Eur J Pediatr* 155:237–244
- Pranzatelli MR, Tate ED, Dukart WS, Flint MJ, Hoffman MT, Oksa AE (2005) Sleep disturbance and rage attacks in opsoclonus-myoclonus syndrome: response to trazodone. *J Pediatr* 147:372–378
- Pranzatelli MR, Tate ED, Kinsbourne M, Caviness VS Jr, Mishra B (2002) Forty-one year follow-up of childhood-onset opsoclonus-myoclonus-ataxia: cerebellar atrophy, multiphasic relapses, and response to IVIG. *Mov Disord* 17:1387–1390
- Pranzatelli MR, Tate ED, Travelstead AL, Longee D (2005) Immunologic and clinical responses to rituximab in a child with opsoclonus-myoclonus syndrome. *Pediatrics* 115:e115–e119
- Pranzatelli MR, Travelstead AL, Tate ED, Allison TJ, Moticka EJ, Franz DN, Nigro MA, Parke JT, Stumpf DA, Verhulst SJ (2004) B- and T-cell markers in opsoclonus-myoclonus syndrome: immunophenotyping of CSF lymphocytes. *Neurology* 62:1526–1532
- Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 123:1051–1061
- Rudnick E, Khakoo Y, Antunes NL, Seeger RC, Brodeur GM, Shimada H, Gerbing RB, Stram DO, Matthay KK (2001) Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies—a report from the Children's Cancer Group Study. *Med Pediatr Oncol* 36:612–622
- Schmahmann JD, Sherman JC (1998) The cerebellar cognitive affective syndrome. *Brain* 121:561–579
- Tate ED, Allison TJ, Pranzatelli MR, Verhulst SJ (2005) Neuroepidemiologic trends in 105 US cases of pediatric opsoclonus-myoclonus syndrome. *J Pediatr Oncol Nurs* 22:8–19
- Tellegen PJ, Winkel M, Wijnberg-Williams BJ (1996) Snijders-Oomen Non-verbaler Intelligenztest SON-R 212-7. Swets&Zeitlinger, Amsterdam/Lisse
- Tewes U (1999) Hamburg-Wechsler-Intelligenztest für Kinder III. HAWIK-III. Hans Huber, Bern